REMARKS

In order to place the application in condition for allowance, applicants propose canceling claims 26-64 and adding new claims 65-108.

The new claims are directed to compositions comprising a recombinant DNA coding for an adenoviral gp19k. As noted by the Examiner at pages 3-4 of Paper No. 19, applicants have enabled and demonstrated the use of adenoviral genes in conjunction with the claimed compositions and methods. Furthermore, the gp19k encoding sequence is specifically exemplified in the specification (*see* the Ad-βgal-gp19k noted by the Examiner at page 4 of Paper No. 19, and the drawings and Examples in the specification, for example). Additional support for these claims can be found in the specification as a whole and at, for example, page 13, lines 6-15, where the adenoviral genes of the E3 region are described and gp19k is specifically listed. Ad 5 and Ad 2 adenoviral vectors are noted at page 23, lines 11-16 of the specification. Furthermore, naturally occurring strains of adenovirus may include differing gp19k sequences and mutagenesis of those sequences is clearly within the skill of the ordinary artisan. The specification specifically notes site-directed mutagenesis at page 31, line 28, through page 32, line 4. Thus, the new claims also recite mutants of gp19k compared to the wild type Ad 5 sequence, where, as recited in the new claims, the mutants have immunosuppressive function. Applicants also note that the specification at, for example, page 18, lines 15-20, indicates that genes with similar functional properties can be obtained by any technique known to a person skilled in the art and then used to construct the vectors of this invention, which would include gp19k mutants as recited. As stated in the last Office Action (*see* page 3 and the sentence bridging pages 4-5), applicants have demonstrated that the adenoviral gp19k sequence can be used to prolong cell survival, in one example. Any gp19k protein with similar

immunosuppressive functions will predictably employ the same mechanism and allow one to make and use the claimed invention. Applicants submit that the new claims find clear support in the specification and original claims.

The cancellation of claims and presentation of new claims is not an admission or acquiescence to the concerns stated by the Examiner and is not done for reasons related to patentability. Applicants have broadened the claims by including first and second recombinant DNA where, as recited in the new claims, the DNA can encode a protein, a ribozyme, or an antisense RNA. No new matter enters by these amendments. Applicants request entry of the amendment, reconsideration of the application, and timely notice of allowability.

Rejection under 35 U.S.C. § 112, second paragraph.

Claims 61-64 stand rejected under 35 U.S.C. § 112, second paragraph. The Examiner asserts that claims 61-64 are incomplete as allegedly omitting essential steps.

Although the preamble of claim 61 indicates that the gene of interest is expressed in the cell ("A method of prolonging the survival of a cell expressing a gene of interest...", *see* previous claim 61), the examiner argues that this is insufficient to indicate whether the survival of the cell has been prolonged. Applicants traverse this rejection and contend that claims should be read in light of the specification and with the reasonable understanding of one skilled in the art. Taking into account these factors, applicants respectfully submit that one of skill in the art would need no further recitations in these claims in order to understand them.

In response to the examiner's objection, however, applicants have amended the application to contain new claims. Applicants respectfully submit that claims 102-108 are enabled by the specification and fully meet the requirements of 35 U.S.C. § 112, second

paragraph. The language of new claim 102 clarifies the link between the method indicated and prolonged cell survival. This amendment is not made for reasons related to the patentability of the claims and applicants relinquish no subject matter by making this amendment. Applicants request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph.

Claims 26-64 stand rejected under 35 U.S.C. § 112, first paragraph. In particular, the Examiner contends that the specification does not reasonably provide enablement for a composition comprising any immunosuppressive agent and a recombinant adenovirus containing a therapeutic gene and any immunoprotective gene, and a method for expression of a therapeutic gene using said composition. Applicants respectfully disagree.

Applicants submit that the specification does reasonably provide enablement for a composition where an adenovirus sequence comprises a sequence coding for an immunoprotective protein, such as a sequence coding for adenoviral gp19k, as well as for a method for expression of a first recombinant DNA encoding a sequence of interest using this composition. Applicants have previously submitted evidence supporting the enablement of the claims (*see* Response to Paper No. 13 and the papers submitted and discussed). Applicants also incorporate by reference the comments submitted at pages 5-9 in the Response to Paper No. 13 as well as the comments submitted at pages 3-6 in the Reply to Office Action (Paper No. 16).

In their Response to Paper No. 13, applicants addressed the statutory standard applicable and the lack of evidence contrary to applicants' assertions of enablement. Applicants contend that a *prima facie* case of enablement has not been made by the examiner. The examiner's reasons for rejecting claims 26-64 are not supported by adequate evidence to one skilled in the

art; these claims are adequately enabled by the specification. Absent a showing of why the applicants' presumptively enabled claims and enabling disclosure cannot be made or used, no *prima facie* case of enablement has been presented by the Patent Office.

The examiner cites a Linsley *et al.* document to question whether an immunosuppressive agent, CTLA4Ig, can lead to tolerance of two well-known and potent immunogens. However, as the applicants have stated before in Response to Paper No. 13 (*see* page 7), this document provides no logical barrier to the selection of an immunosuppressive agent in this case. One skilled in the art, when considering the appropriate information from Linsley, would logically conclude that the immune response to cells, such as those infected with a recombinant adenovirus, is effectively blocked by the one immunosuppressive agent discussed.

The examiner also cites a Kay *et al.* document for the proposition that antigen-dependent immunity limits the duration of gene expression from recombinant adenovirus vectors. However, this document, as discussed in Response to Paper No. 13 (*see* page 8), demonstrates that immunosuppressive agents, such as CTLA4Ig, do indeed prolong the expression of genes from adenoviral vectors. The applicants do not need to show that every possible embodiment that falls under the claims actually works in order to show that the claims are enabled. If one skilled in the art can easily determine what the inoperative combinations are, a claim need not specifically exclude the inoperative embodiments in order to be enabled. *W.L. Gore & Associates, Inc. v. Garlock, Inc.* 220 U.S.P.Q. 303, 316 (Fed. Cir. 1983).

The examiner also cites Verma and Eck to support the argument that gene therapy is an unpredictable art. As stated before (*see* Reply to Office Action (Paper No. 16), at pages 4-5), these articles address the clinical effectiveness, optimization of efficacy, and other clinical considerations for gene therapy (*see* page 239, first paragraph of Verma, and Table 5-1 of Eck).

The citation to articles that relate to clinical standards -- which are the realm of the FDA, and not the PTO standard -- at least implies that the only evidence sufficient to dispel the concerns of these articles is clinical trial evidence. That is the type of evidence treated in these papers. Regardless, nothing in these papers says, or would be taken by one of skill in the art to say, that gene therapy is devoid of promising inventions or devoid of any patentable, pharmaceutical properties akin to those discussed in *In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). As discussed in applicants' previous responses, the *In re Brana* decision reversed a PTO rejection that improperly applied an FDA-like standard to an anti-tumor compound instead of the patent law standard.

Viewing all of applicants' arguments and evidence demonstrating enablement, applicants submit that the claims meet the statutory standard for enablement under 35 U.S.C. § 112, first paragraph. Furthermore, the specification contains a detailed description of how to make and how to use a composition comprising an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA comprising a sequence of interest and a second recombinant DNA containing a sequence coding for adenoviral gp19k. Therefore, applicants submit that this rejection is untenable and respectfully request that it be reconsidered and withdrawn.

Conclusion

Applicants believe that this application is now in condition for allowance. If the Examiner believes that prosecution might be furthered by discussing the application with applicants' representative, in person or by telephone, we would welcome the opportunity to do so.

If any extension of time fees, requests for extension of time, or petitions are necessary to enter and consider this paper, applicants hereby petition or request an extension of time. For any fees required, including additional claim fees, in order to enter or consider this paper or keep this application pending, applicants' representative hereby authorizes the Commissioner to charge Deposit Account No. 50-1129. If there is any variance between the fees submitted and any fee required, including the extension of time fee and the fee for net addition of claims, the Commissioner is hereby authorized to charge or credit Deposit Account No. 50-1129.

Respectfully submitted,
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